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(54) INTRALUMINAR PERFORATED RADIALLY EXPANDABLE DRUG DELIVERY PROSTHESIS

INTRALUMINARE, DURCHLÖCHERTE, RADIAL AUSWEITBARE PROTHESE ZUR ZUFUHR VON MEDIKAMENTEN

PROTHESE D'ADMINISTRATION DE MEDICAMENT RADIALEMENT EXTENSIBLE A PERFORATION INTRALUMINALE

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Description

[0001] The present invention relates to radially expandable prostheses for implantation in a lumen comprising a tubular wall produced from sheet metal and showing an inner and an outer surface, which tubular wall is provided with cuts forming solid struts having a predetermined thickness and enabling the prosthesis to expand, said solid struts having a longitudinal direction and showing reservoirs made in said outer surface for containing a therapeutic agent.

[0002] In practice, intraluminal prostheses are generally known. They can be implanted in a lumen, for example an artery, to strengthen, support or repair the lumen. With coronary balloon dilatation for example, often a prosthesis is implanted in the place where a coronary artery is injured or where it tends to collapse. Once implanted, the prosthesis strengthens that part of the artery in a way the blood flow is ensured. A prosthesis configuration which is extremely suited for implantation in a body lumen, is a generally cylindrical prosthesis which can radially expand from a first small diameter to a second larger one. Such prostheses can be implanted in the artery by placing them on a catheter and transporting them through the artery to the desired location. The catheter is provided with a balloon or another expansion mechanism which exerts a radial outwards pressure on the prosthesis so that the prosthesis expands to a larger diameter. These prostheses are sufficiently strong to stay in shape after expansion, even after removal of the catheter.

[0003] Radially expandable prostheses are available in a variety of configurations, in this way an optimal efficacy is ensured in different particular situations. The patents of Lau (US Patent Nos. 5,514,154, 5,421,955, and 5,242,399), Baracci (US Patent No. 5,531,741), Gaterud (US Patent No. 85,522,882), Gianturco (US Patent Nos. 5,507,771 and 5,314,444), Termin (US Patent No. 5,496,277), Lane (US Patent No. 5,494,029), Maeda (US Patent No. 5,507,767), Marin (US Patent No. 5,443,477), Khosravi (US Patent No. 5,441,515), Jessen (US Patent No. 5,425,739), Hickle (US Patent No. 5,139,480), Schatz (US Patent No. 5,195,984), Fordenbacher (US Patent No. 5,549,662) and Wiktor (US Patent No. 5,133,732) all contain a sort of radially expandable prosthesis for implantation in a body lumen.

[0004] The mentioned intraluminal prostheses have some disadvantages. One of these disadvantages is the insufficient hemocompatibility of intraluminal prostheses, when they are implanted intravascularly. They can cause acute or subacute thrombotic occlusions due to thrombus formation resulting in a considerable morbidity and even mortality. Furthermore these prostheses evoke a foreign body reaction with a considerable inflammation all around the prosthesis inducing fibromuscular cellular proliferation and narrowing of the prosthesis. The general object of the present invention is therefore to provide new prostheses which enable to reduce the foreign body reaction against the implanted prostheses.

[0005] Concerning the method of producing such prostheses, EP-A-0 931 520 teaches to start from a thin-walled tubular member, in particular a stainless steel tubing, and to cut this tubing to remove portions of the tubing in the desired pattern for the prosthesis or stent. This cutting process is performed by means of a computer-controlled laser. In order to minimise the heat input by the laser into the prosthesis so as to prevent thermal distortion and other damages to the metal, use is made of a Q-switched Nd/YAG laser which is operated to produce very short pulses (<100 nsec) at a high pulse rate of up to 40 kHz. Further, a gas jet is created co-axially to the laser beam. Notwithstanding the use of a gas jet, a considerable amount of debris, slag or molten material is formed along the edges of the cut which must be removed mechanically or chemically after the cutting operation. This is achieved in EP-A-0 931 520 by soaking the cut stainless tube first for eight minutes in a solution of hydrochloric acid (HCl) and by subsequently electropolishing it in an acidic aqueous solution of sulfuric acid, carboxylic acids, phosphates, corrosion inhibitors and a biodegradable surface active agent with a current density of about 0.06 to 0.23 amps per cm^2. A drawback of such severe chemical and electrochemical polishing processes is that the inner and outer surfaces of the tubular prosthesis may also become attacked.

[0006] The prostheses according to the present invention have a special configuration which enables the prosthesis to release an effective amount of therapeutic agent or medicine over a prolonged period of time, in particular a medicine suppressing the foreign body reaction against the prosthesis increasing thereby also the biocompatibility of the prosthesis. The tubular wall of the prosthesis is provided with cuts forming struts having a predetermined thickness and enabling the prosthesis to expand, the struts having a longitudinal direction and showing reservoirs made in said outer surface for containing the therapeutic agent.

[0007] Such a prosthesis is already disclosed in EP-A-0 950 386. In this known prosthesis, the reservoirs are formed by relatively shallow channels which are laser cut in the outer surface of the prosthesis. A drawback of this known prosthesis is that at the location of the channels the local drug delivery will be much greater than at other locations resulting in a quite non-homogeneous distribution of the therapeutic agent. Another drawback is that the depth of the channels is limited in view of the fact that the presence of the channels have a considerable effect on the radial strength and durability of the prosthesis. Due to the limited depth, the effect of this depth on the period of drug release is consequently also limited.

[0008] The object of the present invention is therefore to provide a new prosthesis which enables to provide a more uniform drug release, to extend this release over a greater period of time, to incorporate the therapeutic agent in the prosthesis with a smaller effect on the radial strength thereof and to further increase the biocompatibility of the pros-

thesis.

[0009] For this purpose. the prosthesis of the invention is characterised in that at least a number of said reservoirs are formed by perforating holes which extend through the solid strut forming in the outer surface of the tubular wall an outer opening and in the inner surface of the tubular wall an inner opening, said outer opening having a width measured perpendicular to said longitudinal direction and a length measured in said longitudinal direction which is substantially equal to said width, the prosthesis, including said perforating holes, being polished electrochemically so that said cuts have a smooth electrochemically polished surface.

[0010] Since the length of the holes is substantially equal to the width thereof, more holes can be provided in the outer surface of the prosthesis, i.e. at shorter mutual distances, so that a more homogenous drug delivery is possible. A further advantage of such shorter holes is that they can be made deeper without affecting the required radial strength of the prosthesis. In this way, it is possible to incorporate more therapeutic agent in the prosthesis and to increase the release period thereof due to the fact that a larger amount of therapeutic agent can be contained in one hole relative to the surface area of the outer opening thereof through which the therapeutic agent is released. The small perforating holes allow to load the prosthesis with a dose of medicine up to a thousand times higher compared to a none perforated prosthesis. In this way a more biocompatible intraluminal prosthesis can be obtained which can also be used as a vehiculum for releasing and or depositing medicines locally. Due to the fact that the prosthesis, including the holes, is polished electrochemically, a further increased biocompatibility is achieved.

[0011] In a preferred embodiment, said holes are cut in the strut, in particular by laser cutting.

[0012] An important advantage of this embodiment is that the holes can be made easily by laser cutting, in particular in accordance with the liquid guided laser cutting technique, by simply directing the laser beam to the desired spot and cutting the hole without any further movement of the laser beam. The diameter of the inner opening of the holes on the inner side of the strut can then simply be controlled by adjusting the total amount of energy of the laser beam, i.e. the pulse width, the duration and the intensity thereof. In other words, the amount of therapeutic agent released towards the inside of the prosthesis can be easily controlled by selecting the desired diameter of the inner openings. The total amount of cutting energy can be increased until the inner opening is substantially as large as the outer opening.

[0013] Other particularities and advantages of the invention will become apparent from the following description of some particular embodiments of the prosthesis according to the present invention. The reference numerals used in this description relate to the annexed drawings wherein:

Figure 1 is a top plan view on a tubular prosthesis which has been cut in its longitudinal direction and pressed into a flat sheet;

Figure 2 shows on a larger scale a portion of the sheet illustrated in Figure 1 and showing additionally the holes provided in the outer surface of the prosthesis;

Figure 3 is a diagram setting forth the different steps followed for the electrochemical polishing of nitinol samples;

Figure 4 is a microscopic picture (680x) showing the roughness of the side surface of a laser cut of the as-received nitinol alloy stent made by means of a conventional laser;

Figure 5 is a microscopic picture (655x) of the nitinol alloy stent illustrated in Figure 4 after having been subjected to the electrochemical polishing process;

Figure 6 and 7 are microscopic pictures (326x) of the overpolished surface of a nitinol alloy stent;

Figure 8 is a microscopic picture (300x) of the bottom surface of an electrochemically polished nitinol alloy stent without pickling;

Figure 9 shows, on a larger scale, a schematic cross-sectional view along lines VI-VI in Figure 2, illustrating a perforating hole with a substantially cylindrical shape;

Figure 10 is a view similar to Figure 9 but showing a perforating substantially conical hole having a substantially circular outer opening and a smaller inner opening;

Figure 11 is a view similar to Figure 10 but the non-perforating conical hole does not extend through the strut but shows a bottom;

Figure 12 and 13 are views similar to the views of Figures 10 and 11 but showing another shape of holes;

Figure 14 is a scanning electron microscope picture (156x) showing a perforating hole of the same type as illustrated in Figure 9;

Figure 15 is a scanning electron microscope picture (156x) showing a perforating hole of the same type as illustrated in Figure 10; and

Figure 16 is a scanning electron microscope picture (625x) showing a non-perforating hole, provided with a bottom, of the same type as illustrated in Figure 11.

1) DESCRIPTION OF THE BASIC DESIGN OF THE ENDOVASCULAR PROSTHESIS

[0014] In general the present invention relates to radially expandable prostheses for implantation in a lumen which

comprise a tubular wall produced from sheet metal and showing cuts enabling the prosthesis to expand. These cuts are at least partially made by means of a laser beam. The prosthesis is thus made starting from a tubular member wherein cuts are made, or wherein usually portions are cut away, according to the design of the prosthesis. Instead of starting from a tubular member, use could also be made of a flat sheet which is enrolled and welded together to form the tubular prosthesis. Figures 1 and 2 illustrate a preferred embodiment of a radially expandable prosthesis that presents little or none axial shortening at radial expansion. The prosthesis consists of filaments or struts 1 describing the outline of a cylindrical contour. Each prosthesis filament connects to a separate surface at right angles to a central axis of the cylindrical contour of the prosthesis and parallel with other surfaces of the adjacent filaments. The prosthesis can exist of a variable amount of filaments which all constitute the prosthesis. At least two filaments are necessary, including a first and a second ending filament to determine the extremities of the prosthesis contour.

[0015] These filaments all show a waving contour in the shape of consecutive omegas. Consequently each filament is composed of a number of turns with lowest points and tops zigzag crossing over the length of each filament. The lowest point is the most distant from the adjacent filament and the top is the most closely situated to the adjacent filament. Figure 1 shows a typical configuration with 12 turns, a number that can vary from 3 to 36 turns. The size of each filament, provided as the distance between lowest point and top, changes when the prosthesis expands radially, mostly the size diminishes. In Figure 1 a typical configuration is shown with a distance of 1.5 mm between the lowest point and top, this distance however can vary from 0.5 to 5 mm.

[0016] The end filaments are attached to adjacent intermediate filaments by means of connecting parts in the shape of an omega that act as axial elements joining two adjacent filaments. Such connecting parts are also able to fasten together intermediate filaments. Each connecting part is attached to the adjacent filaments with a first connection point to the one end of the connecting piece and a second one to the other end. Both connecting points are situated in the tops of the filaments. Thus the connecting points are bridging the distance/opening between adjacent filaments with the interstice as maximal width. Not necessarily all perforations are bridged with axial connecting parts. Separate outlined intermediate elements can be joined together by means of junctions that are connected with the intermediate elements on locations distant of the lowest points. Depending on the flexibility needs of the prosthesis a variable number of tops can be provided with connecting parts that link adjacent filaments. In case a higher flexibility is necessary, more tops will stay empty with only one connecting piece between two adjacent filaments. The prosthesis is constructed as such that during gradual expansion of the prosthesis the filament waves will in a first phase become somewhat larger and than gradually become shorter: To compensate for this shortening the omega shaped interconnections will gradually enlarge resulting in a less axial shortening during gradual expansion.

2) ELECTROCHEMICAL POLISHING OF A METALLIC INTRALUMINAL PROSTHESIS : BASIC PRINCIPLES

[0017] Electropolishing is a process by which metal is removed from a work piece by passage of electric current when the work piece is immersed in a liquid media (electrolyte). The work piece is connected to the anodic terminal, while the cathodic terminal is connected to a suitable conductor. Both anodic and cathodic terminals are submerged in the solution, forming a complete electrical circuit. The current applied is direct (DC) current. In this process, the work piece is dissolved, adding metal ions to the solution. When a current passes through the electrolyte, a liquid layer of anodic dissolution products is formed on the surface of the anode; this layer has a higher viscosity and greater electrical resistivity than the bulk of the electrolyte. The thickness of the liquid layer on a rough surface differs from site to site. The current density is non-uniform as result of such non-uniform liquid layer; i.e. it is higher on peaks than in crevices. Thus, peaks dissolve more rapidly than crevices, this, therefore, produces a surface-levelling effect.

[0018] Furthermore electrochemical polishing results in a superficial oxide layer (passivation) which plays also an important role in the biocompatibilisation of a foreign body.

[0019] The quantity of metal removed from the work piece is mainly proportional to the amount of current applied and the time during which the current is applied. In addition, the geometry of the work piece can affect the distribution of the current and, consequently, has an important bearing upon the amount of the metal removed in local area.

[0020] Before electropolishing, the surfaces are preferably degreased and cleaned in organic solvents or by chemical etching in suitable solutions. Stirring is used in cases that the anode is coated with some soluble films or it is necessary to remove bubbles adhering to the surface. Stirring of the electrolyte requires an increase in the current density. The cathodes used in electropolishing should not be attacked in the polishing solution. The surface area of the cathode is preferably much greater than the surface area of the polished work piece. This ensues a more uniform current distribution, reduces cathodic polarisation and reduces power losses. After the electropolishing, the work pieces should be washed with water or other solvents in order to remove residues of the electrolyte or the anodic dissolution products.

NITINOL

[0021] For nitinol a pre-treatment using a solution of 2 ml of hydrofluoric acid and 40 ml of nitric acid (14 M) for 5 to

7 minutes is suggested. For electrochemical polishing optimal results were found with 5 ml of perchloric acid (70%) and 100 ml of acetic acid (99,8%) using an anodic current of 0.15 amp and a voltage of 20 V during 1 to 3 minutes.

TANTALUM

[0022] For tantalum a solution of 20 ml of acetic acid, 50 ml of hydrosulphate and 10 ml of hydrofluoride or a solution of 90 ml of hydrosulphate and 10 ml of hydrofluoride was used. The voltage was 5 V during a period of 1 to 5 minutes and the pre-treatment was done using a solution of 5.6 ml of hydrofluoride (48-51%), 1 ml of hydrosulphate (95-97%), 8 ml of hydronitrate and 8 ml of water during 5 to 7 minutes.

3) A LOCAL INTRALUMINAL MEDICINE OR GENE RELEASING SYSTEM

[0023] Several trials with systemically (oral or intravenous) administered anti restenotic medicines after dilatation of narrowed lumina (for example of a coronary arterial atherosclerotic narrowing) failed in consequence of a too limited medicine concentration on the place where the medicine has to act and due to the systemic medicine's side effects when higher doses are administered. For this reason medicines were applied locally, at the place of the organ to be treated. For example in the treatment of coronary stenoses using special catheters, medicines were injected into the vessel wall.

[0024] Disadvantages of this approach are the limited efficiency of the so called local treatment (less than 5% of the administered medicine reaches the target organ) and the increased damage to the target organ due to the local drug administration.

[0025] Another method is the covering of an endoluminal prosthesis with a polymer coating and the impregnation of the polymer with a medicine. The disadvantage of this method is the limited capacity of the coating and the too fast release of the medicine.

[0026] To optimize this system the present inventors have made holes in the endoluminal prosthesis which holes have either a bottom or extend through the prosthesis. These holes are filled with the medicine impregnated polymer before implantation. The holes can vary in size and density. The condition is that the radial force of the prosthesis is not affected. By applying this technique an increment of the local medicine capacity of the prosthesis with a factor of one hundred and a considerable prolongation of the duration of medicine release can be obtained (weeks instead of days). Animal experimental research showed a hundredfold tissue concentration of the medicine in a porcine model after implantation of a polymer coated perforated endoluminal prosthesis in coronary arteries.

[0027] Furthermore the duration of medicine release was significantly longer and the presence of the medicine in the vascular tissue was significantly longer.

[0028] Polymeric drug eluting surface coatings have been described to improve stent biocompatibility by locally releasing the drug at the target site (EP-A-0 623 354). Disadvantages of this system are:

1) the moderate biocompatibility of the polymers used, resulting in an increased inflammatory reaction,
2) because only very thin polymer layers can be used and the contact area is large, the drug release using these coated stents is too fast and because only very thin polymer layers can be applied the total dose of drug loaded on the stent to be locally released is limited

[0029] By making holes in the metal structure of the prosthesis, which holes show either a bottom or extend right through the metal structure of the prosthesis, (Figure 2) and filling these holes with a drug or a polymer coating containing one or more medicines with anti thrombotic and/or anti restenotic properties, a prosthesis is developed that very efficiently releases the medicine gradually and puts the medicine directly in contact with the damaged tissue. The prosthesis starts to function as a reservoir for the medicine, which is gradually released after implantation of the endoluminal prosthesis to carry out its function.

[0030] Instead of conventional medicines also genes can be used that code for certain substances (proteins) having either an anti thrombotic or an anti restenotic action.

[0031] Three significant advantages are obtained by using the prosthesis provided with holes in comparison with the classical polymer covered prostheses:

1) The total dose of medicine that can be loaded onto the prosthesis increases with a factor of one hundred to one thousand, depending on the size and the amount of holes.
2) By making holes showing a bottom, i.e. non-perforating holes, the medicine release can be directed; either towards the tissue surrounding the lumen or towards the lumen itself.
3) The release time of the medicine becomes much longer (weeks instead of days).

[0032] After having made the prosthesis, the therapeutic agent, i.e. a medicine or genes is to be applied onto the prosthesis, in particular into the holes provided on its surface. This can be done by dipping and/or spraying, after which the therapeutic agent applied next to the holes can optionally be removed. The therapeutic agent can either be applied as such or as a solution. In a preferred embodiment, it is however combined with a polymer which increases the adherence to the prosthesis and which can be used to control the release properties of the therapeutic agent. In a preferred embodiment there is applied to the body of a prosthesis and in particular to its tissue-contacting outer surface, a solution which includes a solvent, a polymer dissolved in the solvent and a therapeutic substance (i.e. a drug) dispersed in the solvent, and the solvent thereafter is evaporated to leave a drug eluting polymeric substance filling the holes of the prosthesis. The inclusion of a polymer in intimate contact with a drug filling up the holes of the prosthesis allows the drug to be retained in the prosthesis in a resilient matrix during expansion of the prosthesis and also slows the administration of drug following implantation. This method can be used whether the perforated prosthesis has a metallic or polymeric surface. The method is also an extremely simple one since it can be effected by simply immersing the perforated prosthesis into the solution or by spraying the solution onto the perforated prosthesis. The amount of drug to be included in the perforated prosthesis can be readily controlled by changing the size and the amounts of the holes and/or perforations or by using different drug concentrations and or different coating application methods. The rate at which the drug is delivered can be controlled by the selection of an appropriate bioabsorbable or biostable polymer and by the ratio of drug to polymer in the solution. By this method, drugs such as glucocorticoids (e.g. methylprednisolone, dexamethasone, betamethasone), heparin, hirudin, tocopherol, angiopeptin, aspirin, ACE inhibitors, Cytochalasin A, B, and D, Trapidil, Paclitaxel, Rapamycin, Actinomycin, growth factors, oligonucleotides, and, more generally, antiplatelet agents, anticoagulant-agents, antimitotic agents, antioxidants, antimetabolite agents, and anti-inflammatory agents and also genes can be stored in a perforated prosthesis, retained in a perforated prosthesis during expansion of the perforated prosthesis and elute the drug at a controlled rate. The release rate can be further controlled by using additional barrier coatings or multiple layers of coating with varying drug concentrations. In operation, the perforated prosthesis made according to the present invention can deliver drugs to a body lumen by introducing the perforated prosthesis transluminally into a selected portion of the body lumen and radially expanding the perforated prosthesis into contact with the body lumen. The transluminal delivery can be accomplished by a catheter designed for the delivery of perforated prostheses and the radial expansion can be accomplished by balloon expansion of the perforated prosthesis, by self-expansion of the perforated prosthesis or a combination of self-expansion and balloon expansion.

[0033] The underlying structure of the perforated prosthesis used according to the invention can be virtually any perforated prosthesis design, for example of the self-expanding type or of the balloon expandable type, and of metal or polymeric material. Thus metal prosthesis designs such as those disclosed in US-A-4 733 665 (Palmaz) and US-A-5 603 721 (Lau) could be used in the present invention. The perforated prosthesis could be made of virtually any biocompatible material having physical properties suitable for the design. For example, tantalum, nitinol and stainless steel have been proven suitable for many such designs and could be used in the present invention. Also, prostheses made of biostable or bioabsorbable polymers such as poly(ethylene terephthalate), polyacetal, poly(lactic acid), poly (ethylene oxide)/poly(butylene terephthalate) copolymer could be used in the present invention. Although the perforated prosthesis surface should be clean and free from contaminants that may be introduced during manufacturing, the perforated prosthesis surface requires no particular surface treatment in order to retain the coating applied in the present invention.

[0034] To coat the perforated prosthesis, in particular to fill the holes made therein, the following method can be followed. A solution which includes a solvent, a polymer dissolved in the solvent and a therapeutic substance dispersed in the solvent is first prepared. The solvent, polymer and therapeutic substance should be mutually compatible. The solvent should be capable of placing the polymer into solution at the concentration desired. Moreover the solvent and polymer should not chemically alter the therapeutic character of the therapeutic substance. However, the therapeutic substance only needs to be dispersed throughout the solvent so that it may be either in a true solution with the solvent or dispersed in fine particles in the solvent. Examples of some suitable combinations of polymer, solvent and therapeutic substance are set forth in Table 18.

Table 18.

Examples of some suitable combinations of polymers, solvents and therapeutic substances		
Polymer	**Solvent**	**Therapeutic substance**
poly(L-lactic acid)	chloroform	dexamethasone
poly(lactic acid-co-glycolic acid)	acetone	dexamethasone
polyether urethane	N-methyl pyrrolidone	tocopherol (vitamin E)

Table 18. (continued)

Examples of some suitable combinations of polymers, solvents and therapeutic substances		
Polymer	**Solvent**	**Therapeutic substance**
silicone adhesive	xylene	dexamethasone phosphate
poly(hydroxybutyrate-cohydroxy-valerate)	dichloromethane	aspirin
fibrin	water (buffered saline)	heparin

[0035] The solution is applied to the perforated prosthesis and the solvent is allowed to evaporate, thereby filling the perforations and leaving on the perforated prosthesis surface a coating of the polymer and the therapeutic substance. Typically, the solution can be applied to the perforated prosthesis by either spraying the solution onto the perforated prosthesis or immersing the perforated prosthesis in the solution. Whether one chooses application by immersion or application by spraying depends principally on the viscosity and surface tension of the solution. After having coated the prosthesis, the prosthesis can optionally be cleaned to remove the coating applied next to the holes leaving only the therapeutic agent present in the holes onto the prosthesis.

[0036] The polymer chosen should be a polymer that is biocompatible and minimizes irritation to the vessel wall when the perforated prosthesis is implanted. The polymer may be either a biostable or a bioabsorbable polymer depending on the desired rate of release or the desired degree of polymer stability, but a bioabsorbable polymer may be more desirable since, unlike a biostable polymer, it will not be present long after implantation to cause any adverse, chronic local response. Bioabsorbable polymers that could be used include poly(L-lactic acid), polycaprolactone, poly (lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxyburytate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D, L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosoester uethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(etheresters) (e.g. PEO/PLA) polyalkylene oxalates, poly(organs)phosphazenes, hydrophylic polymetracrylates and biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid. Also, biostable polymers with a relative low chronic tissue response such as polyurethanes, silicones, and polyesters could be used and other polymers could also be used if they can be dissolved and cured or polymerized on the perforated prosthesis such as polyolefins, polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidende chloride; polyacrylonitrile, polyvinyl ketones; polyvinyl aromatics, such as polystyrene, polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, actrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyl resins; polycarbonates: polyoxymthylenes; polyimides; polyethers; epoxy resins, polyurethanes; rayon; rayon-triacetate; cellulose, cellulose acetate, cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers, carboxymethyl cellulose and hydrophylic polymetacrylates. The ratio of therapeutic substance to polymer in the solution will depend on the efficacy of the polymer in securing the therapeutic substance into the perforated prosthesis and the rate at which the coating is to release the therapeutic substance to the tissue of the blood vessel or body conduit. More polymer may be needed if it has relatively poor efficacy in retaining the therapeutic substance in the perforated prosthesis and more polymer may be needed in order to provide an elution matrix that limits the elution of a very soluble therapeutic substance. A wide ratio of therapeutic substance to polymer could therefore be appropriate and the weight ratio could range from about 10:1 to 1:100. The therapeutic substance could be virtually any therapeutic substance which possesses desirable therapeutic characteristics for application to a blood vessel or body conduit. This can include both solid substances and liquid substances. For example, glucocorticoids (e.g. methyl prednisolone, dexamethasone, betamethasone), heparin, hirudin, tocopherol, angiopeptin, aspirin, Cytochalasin A, B, and D, Trapidil, Paclitaxel, Rapamycin, Actinomycin, ACE inhibitors, A2 blockers, beta blockers, growth factors, oligonucleotides, and, more generally, antiplatelet agents, anticoagulant agents, antimitotic agents, antioxidants, antimetabolite agents, and antiinflammatory agents could be used. Antiplatelet agents can include drugs such as aspirin and dipyridamole. Anticoagulant agents can include drugs such as heparin, coumadin, protamine, hirudin and tick anticoagulant protein. Antimitotic agents and antimetabolite agents can include drugs such as methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin and mitomycin. Furthermore this perforated prosthesis can be used to deliver genes that code for substances that can influence the foreign body reaction to the prosthesis or modify the healing response induced by tissue damage.

DESCRIPTION OF THE PERFORATED PROSTHESIS IN ORDER TO OBTAIN AN IMPROVED LOCAL DRUG DELIVERY DEVICE

[0037] To illustrate the invention a tubular laser cut balloon expandable stent was used (Figures 1 and 2). Perforating holes of 50 μm were made, i.e. holes extending entirely through the stent, using a water-guided eximer laser (Laser-microjet™) at a frequency of 100 Hz, pulse duration of 0.15 ms and a voltage of 510 volts. In this way the holes can easily be made in the same operation as the cutting of the prosthesis out of the tubular member. Other methods can however also be used to make the holes, for example mechanical die cutting or conventional laser cutting techniques. Figure 14 shows a microscopic picture of a part of the obtained prosthesis. After conventional electrochemical polishing the stents were dipped in a polymer solution in which the drug was dissolved. In this example use was made of a fluorinated polymethacrylate (PFM-P75) in which 10% methyl prednisolone was dissolved. Total loading dose of methyl prednisolone loaded on a PFM-P75-coated non perforated stents was 10μg. Total loading dose of a perforated stent was 3500 μg.

[0038] In vitro release curves of the methyl prednisolone loaded PFM-P75-coated stents showed a gradually release of the methyl prednisolone over 3 weeks compared to 48 hours for the non perforated stents. Implantation of the methyl prednisolone loaded perforated stents in porcine coronary arteries demonstrated perfect biocompatibility of these stents. No inflammation surrounding the stent filaments was found at day 3, day 7 and day 14. At six weeks only a minimal neointimal hyperplasia was found. This invention can be used with all kinds of drug or gene containing polymers and also for direct coating of drugs or genes onto the prosthesis without the use of a polymer.

[0039] In accordance with the present invention, the holes provided in the prosthesis include holes that extend through the prosthesis as in the previous example. Different types of holes are illustrated in the schematic drawings of Figures 9 to 13 and in the microscopic pictures of Figures 14 to 16. As already explained hereabove, the prosthesis comprises a tubular wall which is usually produced from solid sheet metal but which may also be made of a synthetic sheet material. The wall comprises cuts, usually around cut away portions, forming the struts 1 of which the prosthesis is composed. These struts have an outer or convex surface 2, arranged to engage after implantation the inner wall of the lumen, and an opposite inner or concave surface 3. In order to increase the therapeutic agent loading capacity of the prosthesis, holes 4 are made in the outer surface of the tubular wall. Figures 9 to 13 are cross-sectional views through a strut at the location of such a hole 4. As indicated on these figures, the strut has a strut width W and a thickness T, the longitudinal direction of the strut is indicated by reference A in Figure 2.

[0040] At the outer surface of the strut, the holes 4 show an outer opening 5 which is situated at a distance from both longitudinal edges 10 of the strut. This outer opening has a width w measured perpendicular to the longitudinal direction A of the strut and a length l measured in this longitudinal direction. Since the edge of the opening 5 is somewhat bevelled, the width and the length of the opening 5 is to be determined by drawing a line 11 along the inner wall of the hole 4 and determining the point of intersection with the outer surface plane so that the bevel of the upper edge of the hole 4 is not taken into account for determining the width and length of its outer opening 5. The same goes for the inner opening which will be described hereinafter in case of a perforating hole.

[0041] According to this aspect of the invention, the holes in the prosthesis should comprise holes having an outer opening 5, the length l of which should be substantially equal to the width w thereof whilst the hole 4 itself should be a perforating hole extending through the strut 1. In this way, the therapeutic agent is distributed over a number of relatively small holes enabling a homogeneous distribution thereof over the surface of the prosthesis. The total amount of therapeutic agent applied onto the prosthesis can be controlled not only by the number of holes. An advantage of perforating holes is that the surface of the outer opening 5 through which the therapeutic agent can be released is relatively small compared to the volume of the hole so that the duration of the therapeutic agent release can be extended.

[0042] The outer openings 5 have advantageously a width w larger than 10 μm, in particular larger than 20 μm and more particularly larger than 30 μm but smaller than 100 μm, preferably smaller than 60 μm and most preferably smaller or equal to 50 μm. The length of the outer openings 5 is substantially equal to the width w. The opening 5 is in particular preferably substantially circular.

[0043] In a preferred embodiment, the width w of the outer opening 5 comprises at the most 60%, preferably at the most 50%, of the width W of the strut 1. Together with the limited length l of the outer openings 5 this relatively small width enables to increase the depth d of the holes, in particular to provide perforating holes, whilst maintaining the required minimum radial strength of the prosthesis.

[0044] As illustrated in Figure 2, the openings are divided according to the longitudinal directions of the struts, i.e. they are not preferably not arranged next to one another in the transverse direction in order to have a minimal effect on the radial strength of the prosthesis. Preferably, the holes are arranged on substantially constant mutual distances to achieve a uniform distribution of the therapeutic agent.

[0045] Figures 9 and 14 illustrate a perforating hole 4 forming at the inner surface 3 of the tubular prosthesis wall an inner opening 6 which is substantially as large as the opposite outer opening 5. Apart from the bevelled edges, the

hole 4 is substantially cylindrical. Such a hole 4 can easily be made by means of a laser beam, preferably by means of a liquid-guided laser beam by applying a total amount of cutting energy sufficient to produce such a hole without having to move the laser beam.

[0046] Figures 10, 12 and 15 illustrate a perforating hole 4 which also form an inner opening 6 but which has the advantage that there is a more directional release of the therapeutic agent, i.e. more therapeutic agent is released towards the wall of the lumen than towards the interior thereof. This is due to the fact that the inner opening 6 is smaller than the outer opening 5. In figure 10, the hole narrows conically from the outer opening 5 towards the inner opening 6 and is thus substantially conical. In figure 12, the hole shows on the contrary first a substantially cylindrical portion 7 and subsequently a bottom portion 8 narrowing conically towards the inner opening 6. These two types of holes can also easily be made by means of a laser beam, preferably by means of a liquid-guided laser beam, without having to move the laser beam during the cutting operation. The different types of holes can in particular be controlled by adjusting the pulse width of the pulse laser beam, a greater pulse width producing a more elongated cone shape as in Figure 10 whilst a smaller pulse width produces a shorter or steeper cone shape as in Figure 12.

[0047] For some of the holes, the total amount of energy of the laser beam can be reduced so that the hole does not extend entirely through the strut but forms a bottom 9. Such a hole is illustrated in Figures 11, 13 and 16. In the illustrated embodiments, the hole is entirely conical or frusto-conical. It will however be clear that the hole could also show a conical bottom part and on top of that a more cylindrical part, depending on the thickness of the strut and the depth of the hole. From the shapes of the conical portions in the figures it will be clear that the hole illustrated in Figure 11 can be achieved by means of a same type of laser beam as the hole illustrated in Figure 10 whilst the hole illustrated in Figure 13 can be achieved by means of the same type of laser beam as the hole illustrated in Figure 12, the total amount of cutting energy, i.e. the duration of the cutting process being of course reduced to achieve a shallower hole.

[0048] The holes illustrated in the figures have all a substantially circular cross-section seen parallel to the outer or inner surface of the prosthesis. For making elongated holes, i.e. holes having a length l larger than their width w, two or more of the above described holes can be made next to one another to achieve one elongated hole.

Claims

1. A radially expandable prosthesis for implantation in a lumen comprising a tubular wall produced from sheet metal and showing an inner (3) and an outer surface (2), which tubular wall is provided with cuts forming solid struts (1) having a predetermined thickness (T) and enabling the prosthesis to expand, said solid struts (1) having a longitudinal direction (A) and showing reservoirs (4) made in said outer surface (2) for containing a therapeutic agent, **characterised in that** at least a number of said reservoirs (4) are formed by perforating holes (4) which extend through the solid strut (1) forming in the outer surface (2) of the tubular wall an outer opening (5) and in the inner surface (3) of the tubular wall an inner opening (6), said outer opening (5) having a width (w) measured perpendicular to said longitudinal direction (A) and a length (l) measured in said longitudinal direction (A) which is substantially equal to said width (w), the prosthesis, including said perforating holes (4), being polished electrochemically so that said cuts have a smooth electrochemically polished surface.

2. A prosthesis according to claim 1, **characterised in that** said outer opening (5) is substantially circular.

3. A prosthesis according to claim 1 or 2, **characterised in that** said width (w) is larger than 10 μm but smaller than 100 μm.

4. A prosthesis according to claim 3, **characterised in that** said width (w) is larger than 20 μm.

5. A prosthesis according to claim 4, **characterised in that** said width (w) is larger than 30 μm.

6. A prosthesis according to any one of the claims 3 to 5, **characterised in that** said width (w) is smaller than 60 μm.

7. A prosthesis according to claim 6, **characterised in that** said width (w) is smaller or equal to 50 μm.

8. A prosthesis according to any one of the claims 1 to 7, **characterised in that** the strut (1) wherein said outer opening (5) is situated has a strut width (W) measured between a first longitudinal edge (10) of the outer surface (2) of the strut (1) and a second longitudinal edge (10) of this outer surface (2), the width (w) of said outer opening (5) comprising at the most 60%, preferably at the most 50%, of said strut width (W).

9. A prosthesis according to any one of the claims 1 to 8, **characterised in that** said holes (4) are divided according

to the longitudinal directions (A) of the struts (1) on these struts, preferably on a substantially constant mutual distance.

10. A prosthesis according to any one of the claims 1 to 9, **characterised in that** said inner opening (6) is smaller than said outer opening (5), at least a bottom portion (8) of said hole (4) narrowing preferably conically towards said inner opening (6).

11. A prosthesis according to claim 10, **characterised in that** said inner opening (6) has substantially the same size as said outer opening (5).

12. A prosthesis according to any one of the claims 1 to 11, **characterised in that** said holes (4) are cut in the strut (1), in particular by laser cutting.

Patentansprüche

1. Eine radial ausdehnbare Prothese zur Implantierung in einem Lumen, die eine röhrenförmige Wand umfasst, welche aus Blech hergestellt ist und eine innere (3) und eine äußere (2) Oberfläche aufweist, wobei die röhrenförmige Wand mit Schnitten versehen ist, welche solide Streben (1) bilden, die eine vorbestimmte Dicke (T) aufweisen und durch die sich die Prothese ausdehnen kann, wobei die soliden Streben (1) eine längliche Richtung (A) haben und Reservoire (4) aufweisen, die in der erwähnten äußeren (2) Oberfläche angebracht sind, um ein therapeutisches Agens zu enthalten, **dadurch gekennzeichnet, dass** zumindest eine Anzahl der erwähnten Reservoire (4) durch perforierende Löcher (4) gebildet sind, die sich durch die solide Strebe (1) ausdehnen, wodurch sie in der äußeren Oberfläche (2) der röhrenförmigen Wand eine äußere Öffnung (5) und in der inneren Oberfläche (3) der röhrenförmigen Wand eine innere Öffnung (6) bilden, wobei die erwähnte äußere Öffnung (5) eine Breite (w) hat, die senkrecht zur erwähnten länglichen Richtung (A) gemessen wird, und eine Länge (l), die in der erwähnten länglichen Richtung (A) gemessen wird und substanziell gleich ist wie die erwähnte Breite (w), wobei die Prothese, einschließlich der erwähnten perforierenden Löcher (4), elektrochemisch poliert sind, sodass die erwähnten Schnitte eine glatte, elektrochemisch polierte Oberfläche aufweisen.

2. Eine Prothese nach Anspruch 1, **dadurch gekennzeichnet, dass** die erwähnte äußere Öffnung (5) substanziell kreisförmig ist.

3. Eine Prothese nach Anspruch 1 oder 2, **dadurch gekennzeichnet, dass** die erwähnte Breite (w) größer als 10 µm aber kleiner als 100 µm ist.

4. Eine Prothese nach Anspruch 3, **dadurch gekennzeichnet, dass** die erwähnte Breite (w) größer als 20 µm ist.

5. Eine Prothese nach Anspruch 4, **dadurch gekennzeichnet, dass** die erwähnte Breite (w) größer als 30 µm ist.

6. Eine Prothese nach einem der Ansprüche 3 bis 5, **dadurch gekennzeichnet, dass** die erwähnte Breite (w) kleiner als 60 µm ist.

7. Eine Prothese nach Anspruch 6, **dadurch gekennzeichnet, dass** die erwähnte Breite (w) kleiner oder gleich 50 µm ist.

8. Eine Prothese nach einem der Ansprüche 1 bis 7, **dadurch gekennzeichnet, dass** die Strebe (1), in der sich die erwähnte äußere Öffnung (5) befindet, eine Strebenbreite (W) hat, welche zwischen einem ersten Längsrand (10) der äußeren Oberfläche (2) der Strebe (1) und einem zweiten Längsrand (10) dieser äußeren Oberfläche (2) gemessen wird, wobei die Breite (w) der erwähnten äußeren Öffnung (5) höchstens 60%, vorzugsweise höchstens 50%, der erwähnten Strebenbreite (W) einnimmt.

9. Eine Prothese nach einem der Ansprüche 1 bis 8, **dadurch gekennzeichnet, dass** die erwähnten Löcher (4) gemäß den Längsrichtungen (A) der Streben (1) auf diesen Streben verteilt sind, vorzugsweise in einer substanziell konstanten Entfernung zueinander.

10. Eine Prothese nach einem der Ansprüche 1 bis 9, **dadurch gekennzeichnet, dass** die erwähnte innere Öffnung (6) kleiner ist als die erwähnte äußere Öffnung (5), wobei zumindest ein unterer Abschnitt (8) des erwähnten

Loches (4) sich vorzugsweise konisch zur erwähnten inneren Öffnung hin verengt.

11. Eine Prothese nach Anspruch 10, **dadurch gekennzeichnet, dass** die erwähnte innere Öffnung (6) substanziell dieselbe Größe wie die erwähnte äußere Öffnung (5) aufweist.

12. Eine Prothese nach einem der Ansprüche 1 bis 11, **dadurch gekennzeichnet, dass** die erwähnten Löcher (4) in die Strebe (1) geschnitten sind, insbesondere durch Laserschneiden.

Revendications

1. Prothèse radialement extensible pour une implantation dans un lumen comprenant une paroi tubulaire faite de métal en feuille et présentant une surface interne (3) et externe (2), dont la paroi tubulaire est munie de découpes formant des entretoises solides (1) ayant une épaisseur prédéterminée (T) et permettant à la prothèse de s'étendre, lesdites entretoises solides (1) présentant une direction longitudinale (A) et montrant des réservoirs (4) fabriqués dans ladite surface externe (2) pour contenir un agent thérapeutique, **caractérisé en ce qu'**au moins un certain nombre desdits réservoirs (4) sont formés par des trous de perforation (4) qui s'étendent au travers de l'entretoise solide (1) formant dans la surface externe (2) de la paroi tubulaire une ouverture externe (5) et dans la surface interne (3) de la paroi tubulaire une ouverture interne (6), ladite ouverture externe (5) présentant une largeur (w) mesurée perpendiculairement à ladite direction longitudinale (A) et une longueur (l) mesurée dans ladite direction longitudinale (A) laquelle longueur est substantiellement égale à ladite largeur (w), la prothèse, comprenant lesdits trous de perforation (4), étant polie électrochimiquement de sorte que lesdites découpes présentent une surface lisse polie électrochimiquement.

2. Prothèse suivant la revendication 1, **caractérisée en ce que** ladite ouverture externe (5) est substantiellement circulaire.

3. Prothèse suivant la revendication 1 ou 2, **caractérisée en ce que** ladite largeur (w) est supérieure à 10 μm, mais inférieure à 100 μm.

4. Prothèse suivant la revendication 3, **caractérisée en ce** en ce que ladite largeur (w) est supérieure à 20 μm.

5. Prothèse suivant la revendication 4, **caractérisée en ce** en ce que ladite largeur (w) est supérieure à 30 μm.

6. Prothèse suivant l'une quelconque des revendications 3 à 5, **caractérisée en ce** en ce que ladite largeur (w) est inférieure à 60 μm.

7. Prothèse suivant la revendication 6, **caractérisée en ce** en ce que ladite largeur (w) est inférieure ou égale à 50 μm.

8. Prothèse suivant l'une quelconque des revendications 1 à 7, **caractérisée en ce que** l'entretoise (1) dans laquelle est située ladite ouverture externe (5) présente une largeur d'entretoise (W) mesurée entre un premier bord longitudinal (10) de la surface externe (2) de l'entretoise (1) et un deuxième bord longitudinal (10) de cette surface externe (2), la largeur (w) de ladite ouverture externe (5) étant au plus 60%, de préférence au plus 50% de ladite largeur d'entretoise (W).

9. Prothèse suivant l'une quelconque des revendications1 à 8, **caractérisée en ce que** lesdits trous (4) sont divisés selon les directions longitudinales (A) des entretoises (1) sur ces entretoises, de préférence sur une distance mutuelle substantiellement constante.

10. Prothèse suivant l'une quelconque des revendications 1 à 9, **caractérisée en ce que** ladite ouverture interne (6) est plus petite que ladite ouverture externe (5), au moins une partie inférieure (8) dudit trou (4) se rétrécissant de préférence de manière conique vis-à-vis de ladite ouverture interne (6).

11. Prothèse suivant la revendication 10, **caractérisée en ce que** ladite ouverture interne (6) présente substantiellement la même taille que ladite ouverture externe (5).

12. Prothèse suivant l'une quelconque des revendications 1 à 11, **caractérisé en ce que** lesdits trous (4) sont coupés dans l'entretoise (1), en particulier par un usinage au laser.

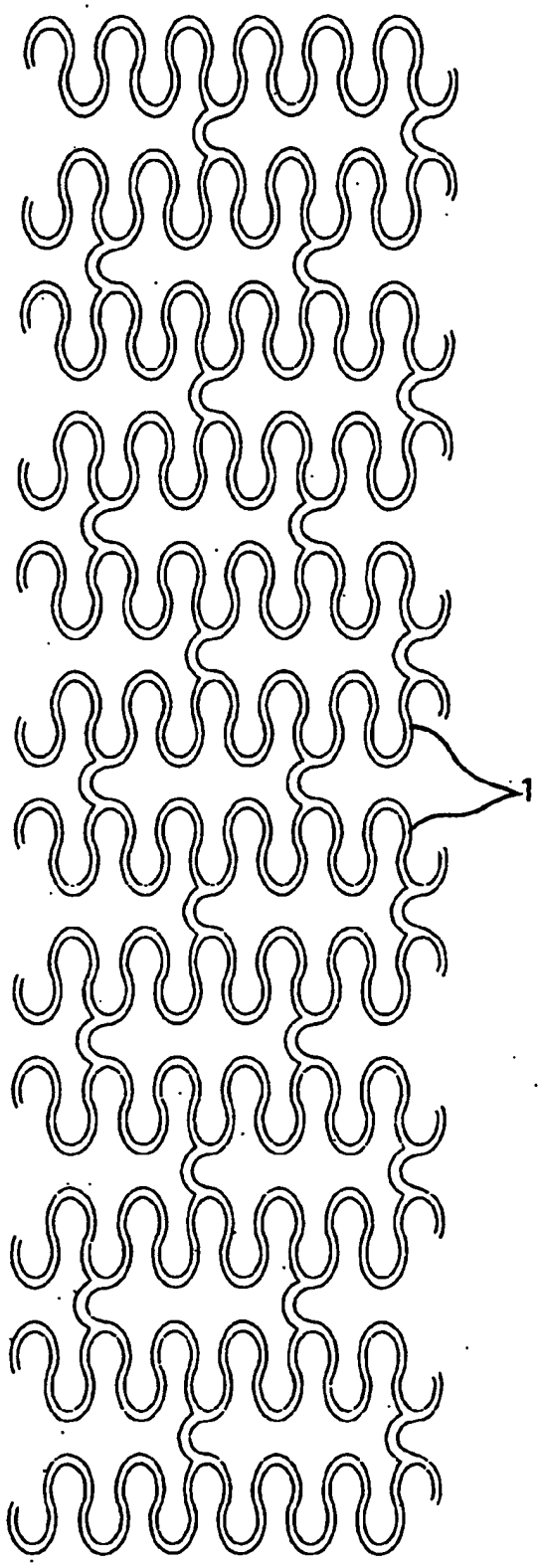

Fig. 1

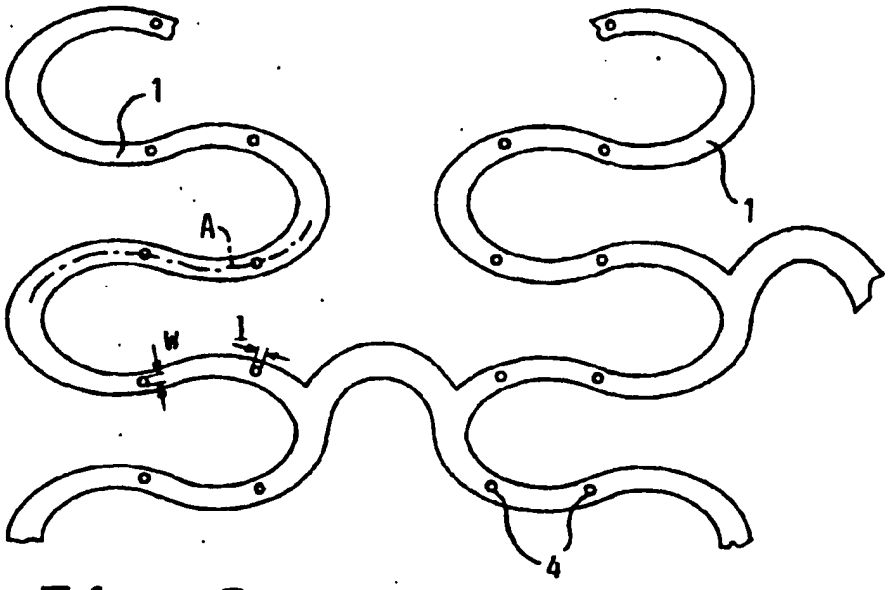
1
A
W
1
1
4

Fig. 2

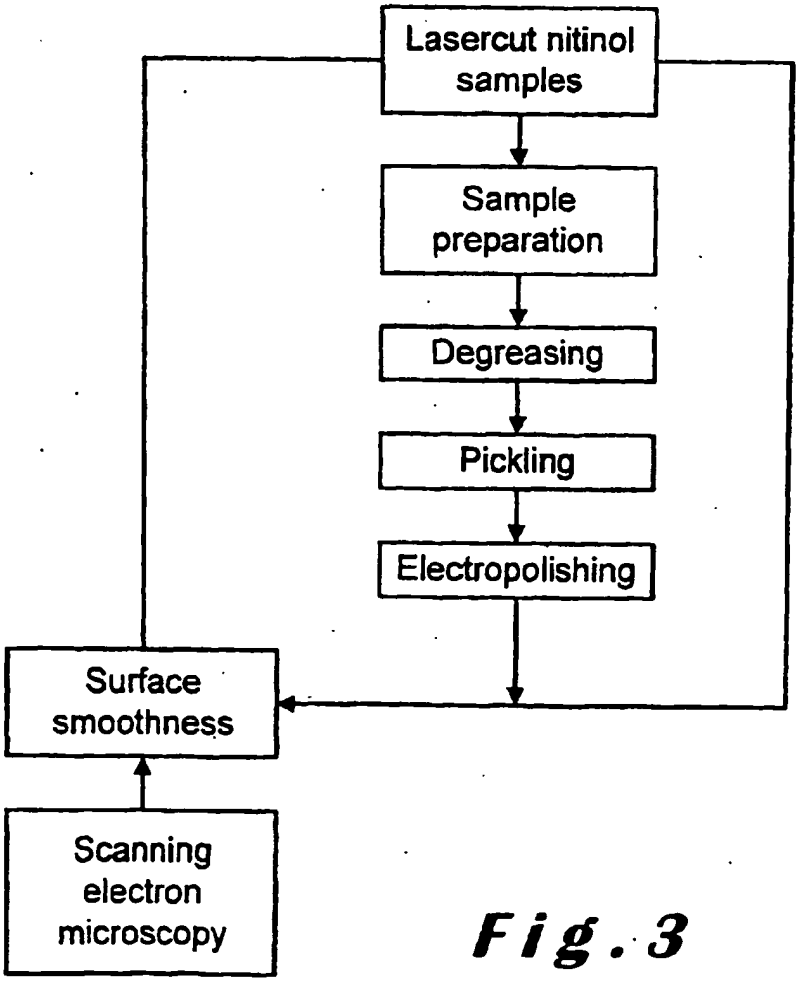
Lasercut nitinol samples
Sample preparation
Degreasing
Pickling
Electropolishing
Surface smoothness
Scanning electron microscopy

Fig. 3

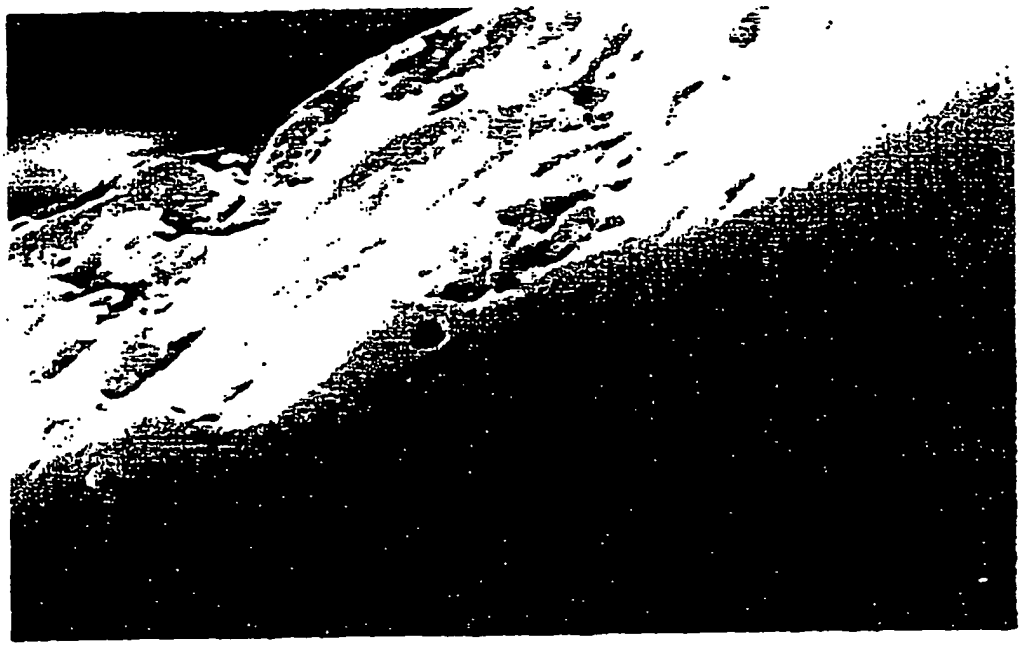

Fig. 4

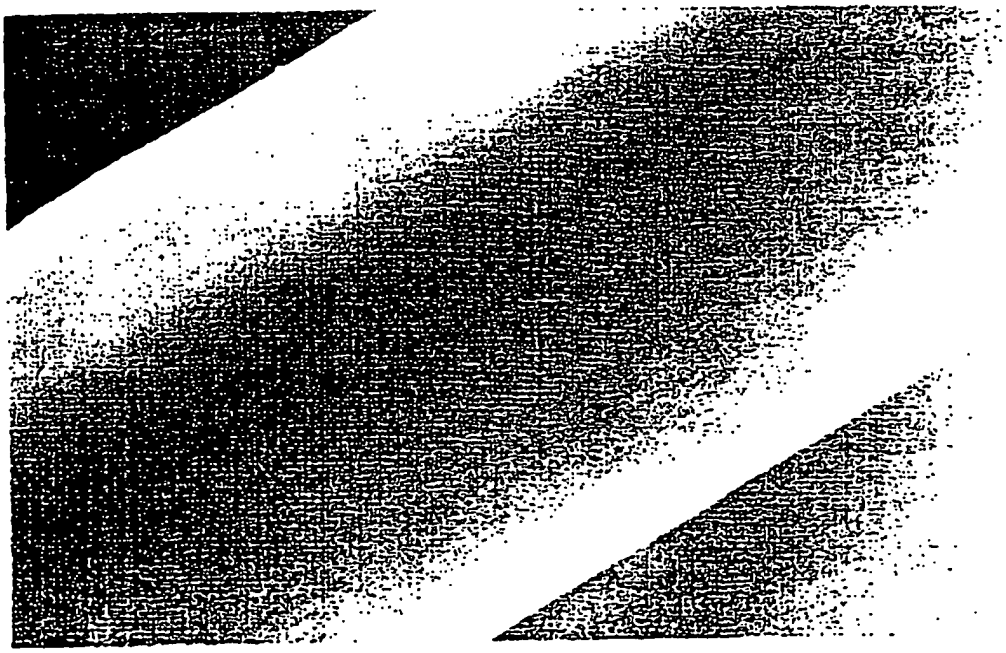

Fig. 5

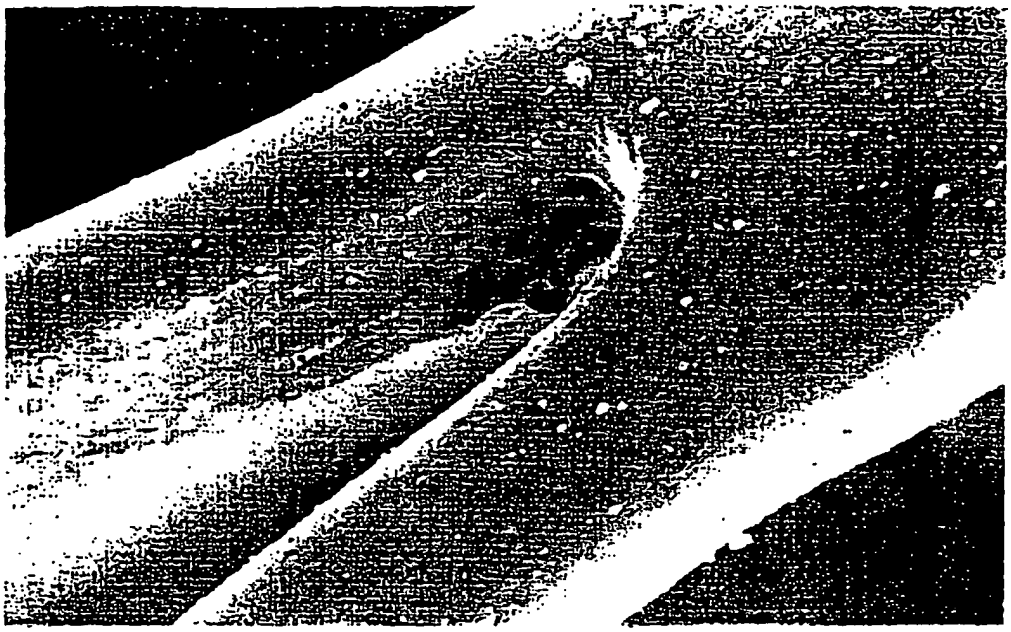

Fig. 6

Fig. 7

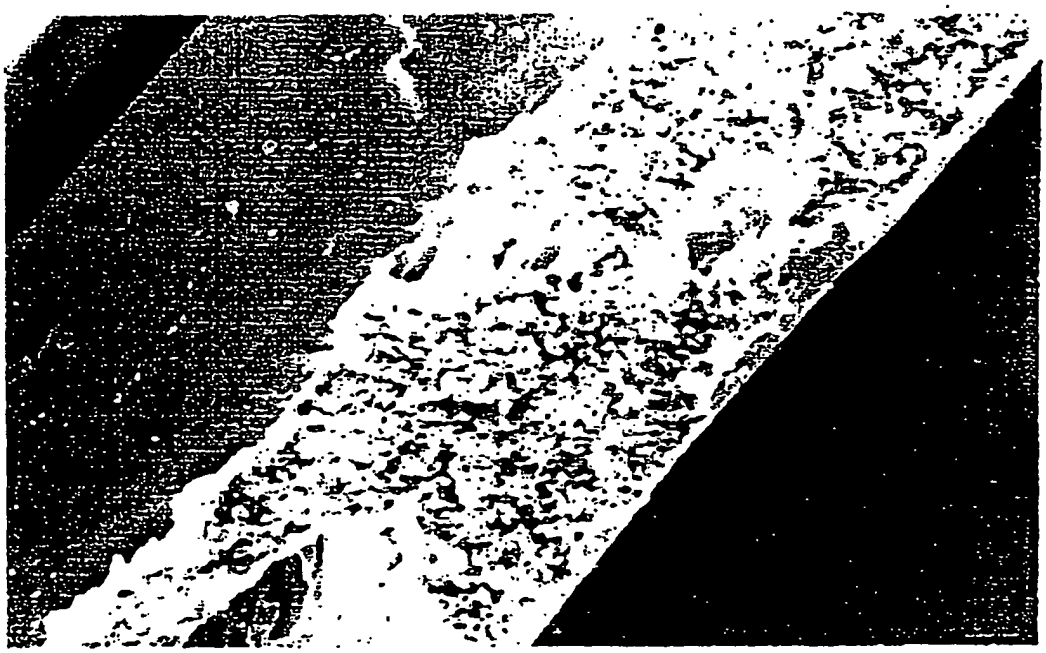

Fig. 8

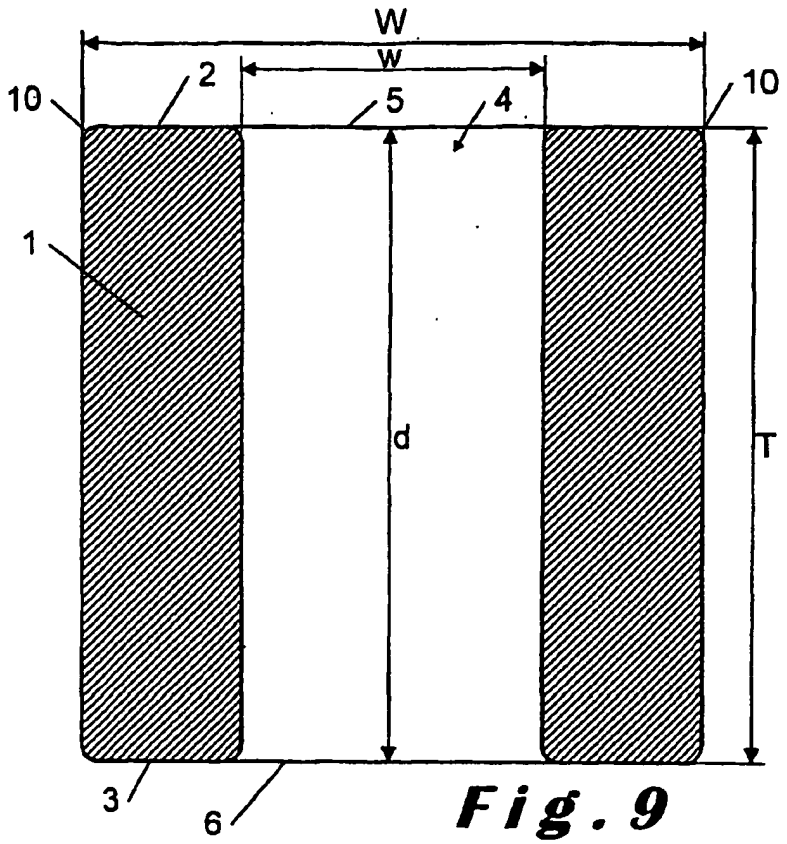

Fig. 9

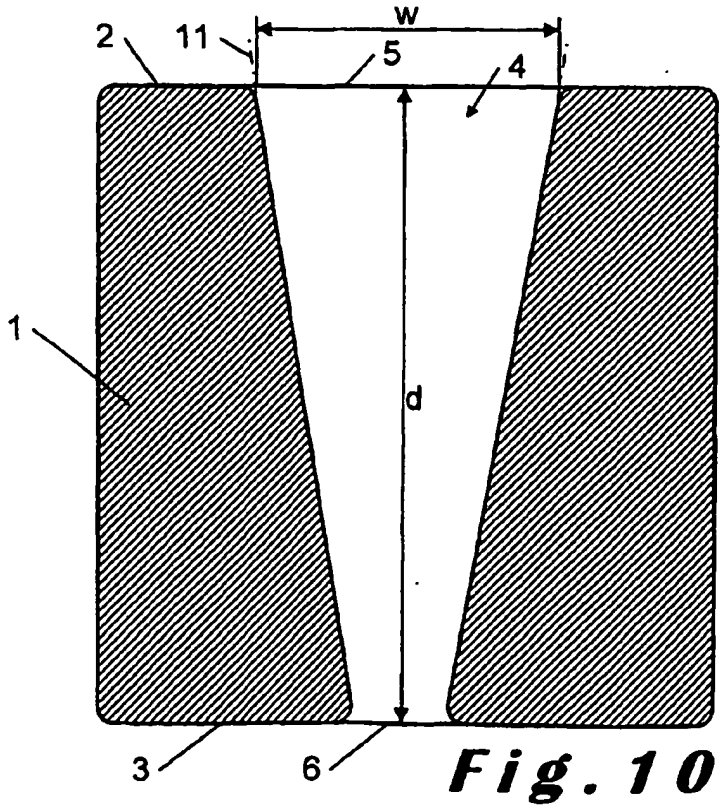

Fig. 10

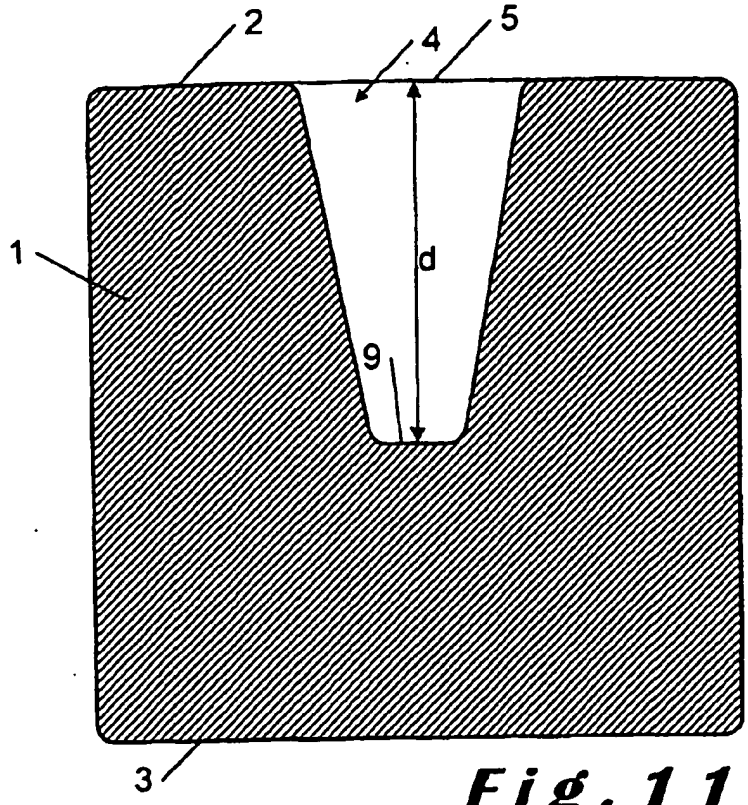

Fig. 11

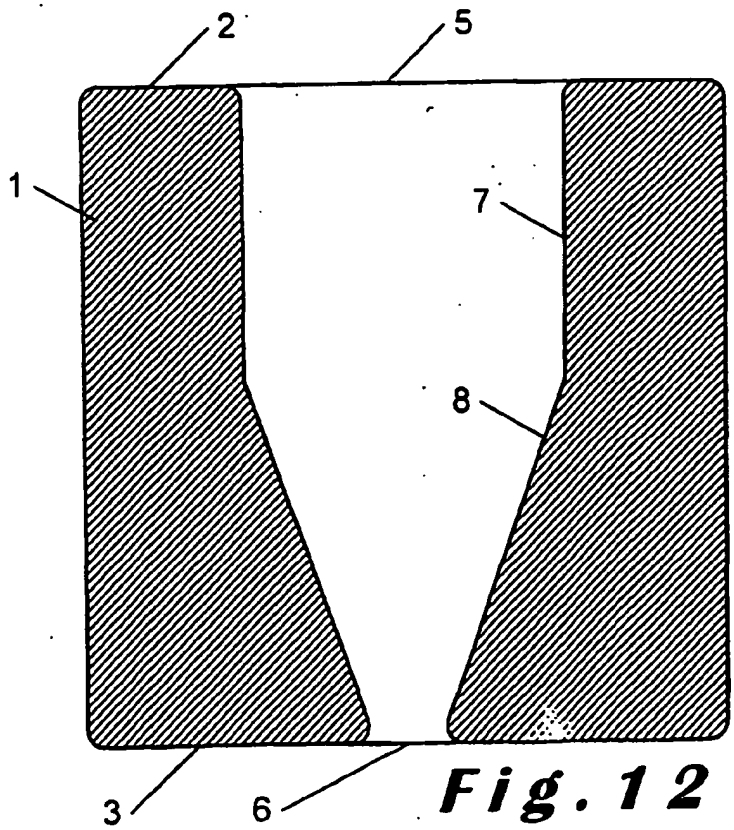

Fig. 12

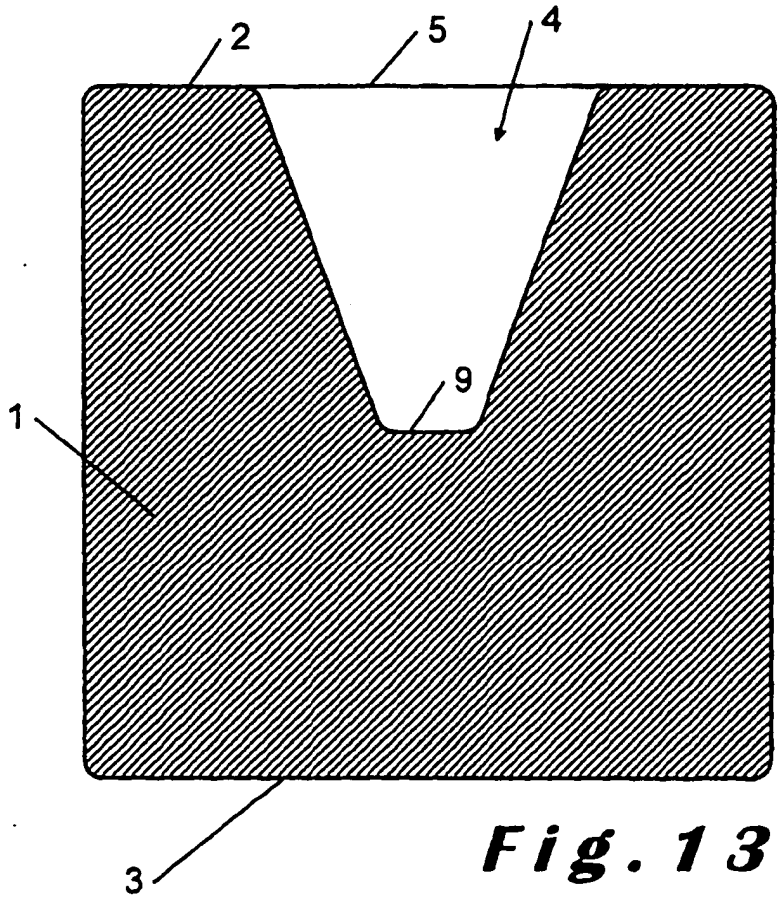

Fig. 13

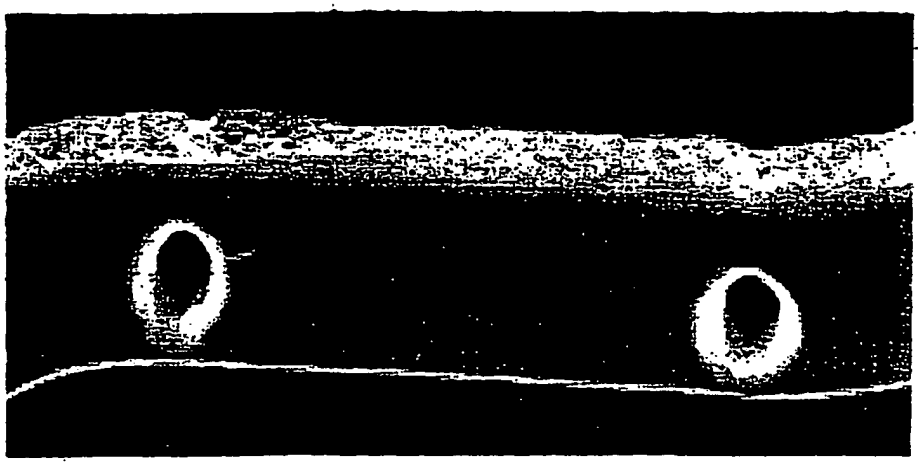

Fig. 14

Fig. 15

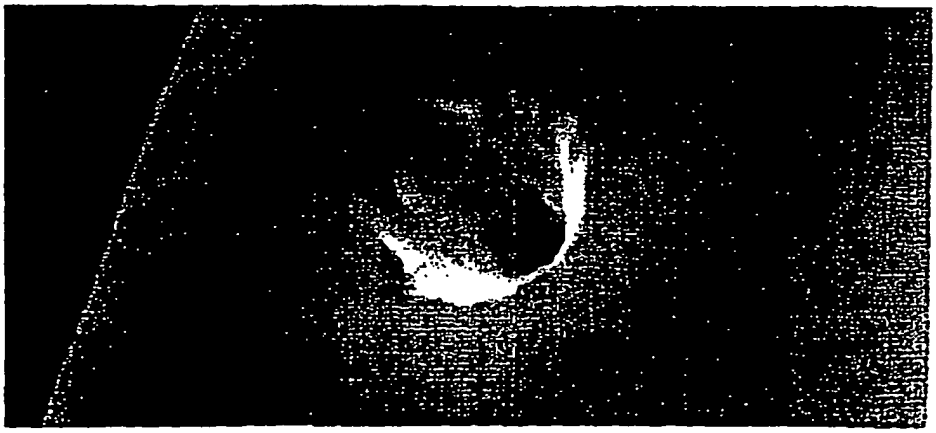

Fig. 16